Paper No.26

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TIMOTHY P. KOGAN, KAIJUN REN,
PETER VANDERSLICE, and PAMELA J. BECK

Appeal No. 2001-0137
Application No. 08/646,558

ON BRIEF

Before WILLIAM F. SMITH, ADAMS and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 32-37, 40-59, and 63. The examiner has indicated that the other pending claims (38, 39, 60, and 61) are "allowable, except for Seq. ID. No. 26." Examiner's Answer, page 24. Claim 32 is representative of the claims on appeal and reads as follows:

> 32. An isolated and purified cyclic peptide of from 5 to about 8 amino acid residues that inhibits the binding of the integrin $\alpha_4\beta_1$ to VCAM-1 or fibronectin, the peptide having (a) an N-terminal amine group, acetyl group or polyethyleneglycol moiety of from about 400 to about 12,000 Daltons average molecular weight linked through an amide bond to the N-terminal residue; and (b) a C-terminal

carboxylic acid or amide group; said peptide being a cyclic disulfide and comprising the amino acid residue sequence of Xaa_1-Xaa_2-Asp-Xaa_3 (SEQ ID NO:15), where Xaa_1, Xaa_2 and Xaa_3 are each independently any aromatic or hydrophobic amino acid residue with the proviso that when Xaa_1 is Lys or Arg, Xaa_2 cannot be Gly or Cys.

The examiner relies on the following references:

Lobl et al. (Lobl)	5,192,746	Mar. 09, 1993
Kogan et al. (Kogan)	5,510,332	Apr. 23, 1996
Nutt et al. (Nutt) (European Patent)	0,422,938	Apr. 17, 1991
Ali et al. (Ali (EP)) (European Patent)	0,341,915	Nov. 15, 1989

Mould et al. (Mould I), "The CS5 Peptide is a Second Site in the IIICS Region of Fibronection Recognized by the Integrin $\alpha_4\beta_1$," Journal of Biological Chemistry, Vol. 266, No. 6, pp. 3579-3585 (1991)

Mould et al. (Mould II), "Identification of a Novel Recognition Sequence for the Integrin α4β1 in the COOH-Terminal Heparin-Binding Domain of Fibronectin," EMBO Journal, Vol. 10, No. 13, pp. 4089-4095 (1991)

Ali et al. (Ali (Peptides)), "Structure-Activity Studies Toward the Improvement of Antiaggregatory Activity of Arg-Gly-Asp-Ser (RGDS)," Peptides: Chemistry, Structure and Biology (Proceedings of the Eleventh Amer. Pept. Symposium), pp. 94-96 (1989)

Aumailley et al. (Aumailley) "Arg-Gly-Asp constrained within cyclic pentapeptides," FEBS Letters, Vol. 291, No. 1, pp. 50-54 (1991)

Davies et al. (Davies), "Synthetic Peptide Mimics of the Active Domain of Fibronectin," Biochemical Society Transactions, Vol. 18, pp. 1326-1328 (1990)

Pierschbacher et al. (Pierschbacher), "Variants of the cell recognition site of fibronection that retain attachment-promoting activity," Proc. Natl. Acad. Sci. USA, Vol. 81, pp. 5985-5988 (1984)

Yamada, "Adhesive Recognition Sequences," Journal of Biological Chemistry, Vol. 266, No. 20, pp. 12809-12812 (1991)

This merits panel relies on the following reference:

Lehninger, "Principles of Biochemistry," Worth Publishers, Inc., New York, pp. 100-103 (1982)

Claims 32-37, 40-59, and 63 stand rejected under 35 U.S.C. § 112, first paragraph, as not supported by either an adequate written description or an enabling disclosure.

Claims 32, 40, and 51 stand rejected under 35 U.S.C. § 102(b) as anticipated by any one of Nutt, Ali (EP), or Lobl.

Claims 32-36, 40, 42-59, and 63 stand rejected under 35 U.S.C. § 103 as obvious in view of the disclosures of either Mould I or Mould II, combined with Ali (Peptides).

Claims 32-36, 40, 42-59, and 63 stand rejected for obviousness-type double patenting over the claims of Kogan '332 and any one of Aumailley, Lobl or Ali (Peptides).

We vacate the rejections of record and enter a new rejection under 37 CFR § 1.196(b).

Discussion

The claims are directed to cyclic peptides that inhibit the binding of integrin $\alpha_4\beta_1$ to, e.g., vascular cell adhesion molecule-1 (VCAM-1), pharmaceutical compositions comprising such peptides, and methods of using the peptides or compositions. Inhibition of integrin $\alpha_4\beta_1$ binding to VCAM-1 is disclosed to be useful in treating various diseases, such as atherosclerosis and rheumatoid arthritis. See the specification, page 2.

The examiner rejected all of claims 32-37, 40-59, and 63 for lack of written description and nonenablement. She also rejected most of these claims as either anticipated by or obvious in view of the prior art, and as obvious variants of the peptides claimed in Appellants' '332 patent.[1] However, we find the claims so indefinite that we cannot reach the merits of the examiner's rejections. We therefore vacate the rejections on appeal and enter the following new ground of rejection.

New Ground of Rejection

Under the provisions of 37 CFR § 1.196(b), we make the following new ground of rejection: claims 32-34, 36, 40, 42-53, 56, 57, and 63 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

Claim 32 is directed to a cyclic peptide comprising, inter alia, the tetrapeptide sequence "Xaa_1-Xaa_2-Asp-Xaa_3 (SEQ ID NO:15), where Xaa_1, Xaa_2 and Xaa_3 are each independently any aromatic or hydrophobic amino acid residue with the proviso that when Xaa_1 is Lys or Arg, Xaa_2 cannot be Gly or Cys." Independent claims 51, 52, and 53 each also contain this language.

The specification in this case does not provide an express definition of which amino acids are considered to be aromatic or hydrophobic. The language of claim 32 itself, however, suggests that at least lysine (Lys), arginine (Arg), glycine (Gly), and cysteine (Cys) are considered to be "aromatic or hydrophobic"

[1] As noted above, the examiner has indicated that claims 38, 39, 60, and 61 are "allowable, except for Seq. ID. No. 26 which contains Lys." Examiner's Answer, page 24. It is unclear from the examiner's statement whether these claims are allowable as written, or are not allowable because they include SEQ ID NO:26. If a claim includes non-allowable subject matter, of course,

amino acids. That is, unless Lys, Arg, Gly, and Cys were considered to be "aromatic or hydrophobic" amino acids, Xaa_1 could never be Lys or Arg and Xaa_2 could never be Gly or Cys, rendering the proviso meaningless. This same proviso is found in the specification. See, e.g., page 3, lines 13-14.[2]

The specification confirms that Lys and Cys are considered to be hydrophobic, and suggests that tyrosine (Tyr) and aspartic acid (Asp) are considered hydrophobic as well. See page 3, lines 12-13 ("Xaa_2 and Xaa_3 are any hydrophobic, L-α-amino acid residue."), page 4, lines 10-12 ("Xaa_2 and Xaa_3 are as defined above. Preferably, . . . Xaa_2 is . . . Lys, . . . or Asp; and Xaa_3 is . . . Tyr."), and page 11 lines 19-20 ("Xaa_2 and Xaa_3 are as defined above. Preferably, . . . Xaa_3 is . . . Cys."). The specification also states that leucine (Leu), isoleucine (Ile), valine (Val), methionine (Met), tryptophan (Trp), and phenylalanine (Phe) are preferred hydrophobic amino acids. See page 3, lines 12-16 ("Xaa_2 and Xaa_3 are any hydrophobic, L-α-amino acid residue. . . . In a preferred embodiment, . . . Xaa_2 is Leu, Ile, Val, . . . or Met and Xaa_3 is Val, . . . Leu, Trp, or Phe.").

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the claim as a whole is not allowable. If the claims are not allowable as written, the proper course of action would be to enter a rejection of the claims under the appropriate statute.

[2] In the specification, Xaa_1 is consistently defined as "any L- or D-α-amino acid residue." See, e.g., page 3, line 12, and page 44 (original claim 1). In the claims on appeal, Xaa_1 is limited to being an aromatic or hydrophobic amino acid. When and if the definiteness issue discussed herein is resolved, the examiner should consider whether the specification provides an adequate written description of the genus of peptides defined by claim 32, especially the limitation of Xaa_1 to aromatic or hydrophobic amino acids. See, e.g., Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000). ("As Ruschig makes clear, one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say 'here is my invention.' In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure.").

Thus, it appears from the claims and specification that applicants consider at least the following amino acids to be hydrophobic: Leu, Ile, Val, Met, Trp, Phe, Tyr, Asp, Lys, Arg, Gly, and Cys. The specification does not define the basis on which these amino acids are considered to be hydrophobic, nor does it define any amino acids as aromatic, or offer any criteria for determining whether other amino acids are hydrophobic or aromatic.

Contrary to what is suggested by the claim language, however, Appellants argue in the Appeal Brief that Arg and Gly are not aromatic or hydrophobic. See page 12 ("Gly is neither aromatic nor hydrophobic.") and pages 13-14 ("'Arg', 'homoArg', 'NmethylArg' and 'norArg' residues . . . all contain large, alkaline (basic) side chains that render those residues highly water soluble and hydrophilic. . . . [N]one of those Arg residues or derivatives thereof are either aromatic or hydrophobic."). Appellants also state in the Appeal Brief that alanine (Ala) is not hydrophobic. See page 16 ("[N]either Gly nor Ala is aromatic or hydrophobic.").

Appellants argue in the Appeal Brief that "the following residues are recognized in the art as being hydrophobic: Val, Leu, Ile, Phe, Trp, Tyr, Cys, and Met." Page 7.[3] As support, they cite a biochemistry textbook by Stryer.[4] No specific pages are cited in the brief, but during prosecution Appellants submitted

[3] Appellants' list of "residues are recognized in the art as being hydrophobic" does not include Lys or Asp, both of which are disclosed in the specification as preferred hydrophobic amino acid residues. See the passages quoted above.
[4] Stryer, Biochemistry, W.H. Freeman & Co., New York, NY, p. 18 (1988). See Exhibit A attached to Paper No. 18 (filed July 31, 1997).

a single page from the cited text. The submitted page states that several amino acids have aliphatic side chains:

> The simplest one is glycine, which has just a hydrogen atom as its side chain. . . . Alanine comes next, with a methyl group as its side chain. Larger hydrocarbon side chains (three and four carbons long) are found in valine, leucine, and isoleucine. These larger aliphatic side chains are hydrophobic—that is, they have an aversion to water. . . .
>
> Proline also has an aliphatic side chain. . . . Proline, often found in the bends of folded protein chains, is not averse to being exposed to water.
>
> Three amino acids with aromatic side chains are part of the fundamental repertoire (Figure 2-11). [The legend to Figure 2-11 states that "[p]henylalanine, tyrosine, and tryptophan have aromatic side chains."]

Stryer, page 18 (emphases in original). Thus, as can be seen, Stryer does not support the proposition for which it is cited by Appellants. Stryer states only that Val, Leu, and Ile are hydrophobic, and either states or implies that Gly, Ala, and Pro are not hydrophobic. The excerpt from Stryer provides no guidance on whether or not the amino acids with aromatic side chains are hydrophobic, and does not discuss any of the other eleven naturally occurring amino acids. In particular, Stryer does not support Appellants' statement that Phe, Trp, Tyr, Cys, and Met are recognized in the art as being hydrophobic.

According to one art-accepted classification system, the hydrophobic (non-polar) amino acids are Ala, Val, Leu, Ile, Pro, Met, Phe, and Trp. See Lehninger, page 101. Lehninger classifies Tyr as "[p]olar but uncharged." Note also that under Lehninger's classification, Gly and Cys are considered polar but

uncharged, Asp is considered negatively charged, and Lys and Arg are considered positively charged. See id.

"It is axiomatic that, in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification and that claim language should be read in light of the specification as it would be interpreted by one of ordinary skill in the art." In re Sneed, 710 F.2d 1544,1548, 218 USPQ 385, 388 (Fed. Cir. 1983) (citation omitted). "[D]uring patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed." In re Zletz, 893 F.2d 319, 322, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989).

Thus, the claim limitation "any aromatic or hydrophobic amino acid residue" must be read as it would be viewed by a person of ordinary skill in the art, as broadly as is reasonable in light of the specification. At the same time, the claims must not be construed so broadly as to abrogate an express limitation. See In re Wilder, 429 F.2d 447, 450, 166 USPQ 545, 548 (CCPA 1970) ("[E]very limitation positively recited in a claim must be given effect in order to determine what subject matter that claim defines."); Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed. Cir. 1993 ("[T]o construe the claims in the manner suggested by TI would read an express limitation out of the claims. This we will not do.").

The issue, therefore, is: how would a person of ordinary skill in the art interpret the claims' reference to "aromatic or hydrophobic" amino acids, in light

of the specification and without reading that limitation out of the claims? Let's review the evidence:

- the claims themselves suggest that "aromatic or hydrophobic" amino acids include Arg, Lys, Gly and Cys;
- the specification suggests that hydrophobic amino acids include Lys, Cys, Tyr, Asp, Leu, Ile, Val, Met, Trp, and Phe;
- the Appeal Brief argues that the hydrophobic amino acids are Val, Leu, Ile, Phe, Trp, Tyr, Cys, and Met, and do not include Gly, Arg, or Ala;
- the text cited by Appellants states that the aromatic amino acids are Phe, Trp, and Tyr, and that the hydrophobic amino acids include Val, Leu, and Ile but not Gly, Ala, or Pro; and
- another textbook states that the hydrophobic amino acids are Ala, Val, Leu, Ile, Pro, Met, Phe, and Trp, and do not include Tyr, Gly, Cys, Asp, Lys or Arg.

Thus, the specification includes as preferred hydrophobic amino acids Leu, Ile, Val, Met, Trp, and Phe, all of which are recognized in the art as hydrophobic. See Lehninger, page 101. However, the specification also includes as preferred "hydrophobic" amino acids Lys and Asp (which are positively and negatively charged, respectively, at pH 7) and Cys and Tyr, which are classified by Lehninger as polar (i.e., hydrophilic).

It is unclear what criteria Appellants are applying in classifying Lys, Asp, Cys, and Tyr as hydrophobic amino acids. Tyr carries a hydroxyl group on its side chain, Cys carries a thiol group, and Lys and Asp carry charged reactive

groups. To classify these amino acids as hydrophobic defies the art-accepted definition of "hydrophobic amino acid."

Thus, while it is clear that Appellants are not using the art-accepted definition of "hydrophobic," it is unclear what definition of "hydrophobic" they are using. It is also unclear what criteria should be used to determine whether other amino acids are hydrophobic. Nor is it clear which amino acids could possibly be considered not hydrophobic, if Appellants' definition of "hydrophobic" amino acids includes those with polar side chains, like Tyr and Cys, as well as those with positively charged (Lys) and negatively charged (Asp) side chains.

Since Appellants are obviously applying a definition of "hydrophobic" that differs from the art-accepted definition, and yet the specification provides no guidance on what their definition of "hydrophobic" is, we find it impossible to determine how the instant claims would be read, in light of the specification, by a person of ordinary skill in the art. Therefore, the claims are indefinite and do not meet the requirements of 35 U.S.C. § 112, second paragraph.

Claims 35, 37-39, 41, 53-55, and 57-61 are not subject to the above new ground of rejection. These claims are directed to peptides (or related compositions or processes) which are defined either by reference to specific SEQ ID NO's or by reciting each of the amino acid residues potentially present in the Xaa_1, Xaa_2 and Xaa_3 positions. The metes and bounds of these claims therefore are readily ascertainable. Although some of these claims were included in the rejections on appeal, we nonetheless find it appropriate to vacate the rejections. The examiner's proffered bases for the rejections are directed to

the broad claims. See, e.g., the Examiner's Answer, page 5 ("The originally disclosed species Phe or Tyr would not provide support for the now broad[ly] claimed 'any aromatic residue.'") and page 6 ("The specification fails to provide enabling disclosure commensurate in scope with the broad[ly] claimed cyclic peptides having amino acid structure comprising or attach[ed] to the recited tetrapeptide."). The examiner has not explained with particularity why the specific peptides of claims 37-39, 41, 60, and 61 or the small genera of peptides recited in claims 35, 53-55, and 57-59 are not adequately described or enabled, or are rendered obvious by the prior art. Therefore, to the extent they were included in the rejections on appeal, the rejections of claims 35, 37-39, 41, 53-55, and 57-61 are vacated.

Other Issues

In the time since the appeal in this case was briefed, Appellants have been issued a patent claiming subject matter that appears to overlap the subject matter of the instant claims. See U.S. Patent 6,087,330. On return of this case, the examiner should consider whether the claims of this case are patentably distinct from those of Appellants' '330 patent. If they are not, a rejection for obviousness-type double patenting would be appropriate in the absence of a terminal disclaimer.

Summary

Claims 32-34, 36, 40, 42-53, 56, 57, and 63 are indefinite when read in light of the specification because it is unclear what amino acids are considered to be "hydrophobic" or "aromatic." We therefore vacate the rejections on appeal and enter a new ground of rejection for indefiniteness.

VACATED, 196(b)

William F. Smith Administrative Patent Judge	))))) BOARD OF PATENT
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